Brief Report

Cardiorespiratory Fitness is Associated with Reduced Risk of Respiratory Diseases in Middle-Aged Caucasian Men: A Long-Term Prospective Cohort Study

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Abstract Cardiorespiratory fitness (CRF), an index of cardiac and respiratory functioning, is strongly associated with a reduced risk of adverse health outcomes. We aimed to assess the prospective association of CRF with the risk of respiratory diseases (defined as chronic obstructive pulmonary disease, pneumonia, or asthma). Cardiorespiratory fitness, as measured by maximal oxygen uptake, was assessed in 1,974 middle-aged men. During a median follow-up of 25.7 years, 382 hospital diagnosed respiratory diseases were recorded. Cardiorespiratory fitness was linearly associated with risk of respiratory diseases. In analysis adjusted for several established and potential risk factors, the hazard ratio (HR) (95% CI) for respiratory diseases was 0.63 (0.45-0.88), when comparing extreme quartiles of CRF levels. The corresponding multivariate adjusted HR (95% CI) for pneumonia was 0.67 (0.48-0.95). Our findings indicate a graded inverse and independent association between CRF and the future risk of respiratory diseases in a general male Caucasian population.

Keywords cardiorespiratory fitness; maximal oxygen uptake; respiratory disease; pneumonia; chronic obstructive pulmonary disease; asthma

Abbreviations

CI Confidence interval

COPD Chronic obstructive pulmonary disease

CRF Cardiorespiratory fitness

HR Hazard ratio

KIHD Kuopio Ischemic Heart Disease

SD Standard deviation

VO_{2max} Maximal oxygen uptake

Introduction

Respiratory diseases such as chronic obstructive pulmonary disease (COPD), pneumonia, and asthma are debilitating diseases of the lungs and airways. Chronic obstructive pulmonary disease is an incurable progressive obstructive lung disease which is characterized by chronic poor airflow.[1] In 2012, COPD was the third leading cause of death globally.[2] Pneumonia affects about 450 million people worldwide and causes approximately 4 million deaths annually.[3] Asthma is a common inflammatory disease of the airways of the lungs and causes about 250,000 to 345,000 deaths annually.[4] Apart from the high mortality rates associated with these respiratory diseases, they are also disabling conditions and account for increased healthcare costs and recurrent hospitalizations. For example, COPD represents three percent of the healthcare spending in Europe.[5] These most common respiratory diseases are caused by an interaction of environmental and genetic risk factors. Major environmental risk factors implicated in their etiology include smoking, exposure to pollution and environmental chemicals with coexisting chronic disease such as diabetes.[5-7] Most cases of these respiratory diseases are potentially preventable through reduction in exposure to underlying risk factors. Physical activity is well established to have important health benefits including the prevention of adverse vascular and non-vascular outcomes[8,9] and has been shown to improve prognosis of patients with respiratory diseases.[10] Cardiorespiratory fitness (CRF), as measured by maximal oxygen uptake (VO_{2max}), is considered the gold standard for assessing aerobic capacity, is an indicator of cardiovascular and pulmonary function, and an index of the level of physical activity.[11] Cardiorespiratory fitness is an established independent risk marker for vascular and non-vascular outcomes.[12] Taken the evidence together, we hypothesized that CRF may be linked to the development of respiratory diseases. We therefore aimed to assess the prospective association of CRF with risk of respiratory diseases, using a population-based cohort of 1,974 middle-aged Finnish men, who were apparently free from any respiratory diseases at baseline.

Methods

The current analyses were based on the Finnish Kuopio Ischemic Heart Disease (KIHD) risk factor study which comprised a representative sample of middle-aged men aged 42-61 years recruited from Kuopio in eastern Finland. The Research Ethics Committee of the University of Eastern Finland approved all study procedures which was conducted according to the Declaration of Helsinki. Each participant provided written informed consent. Details of recruitment methods and measurements of risk markers have been described previously.[13] We assessed CRF using directly measured VO_{2max}, which is considered the gold standard expression of CRF. Repeat measurements were also performed several years apart in a random subset of participants. A detailed description of the measurement of VO_{2max} has been reported elsewhere.[14] Briefly, a maximal symptom-limited exercise tolerance test was performed between 08:00-10:00 hours using an electrically braked cycle ergometer. The standardized testing protocol comprised of an increase in the workload of 20 W/min with the direct analyses of respiratory gases by breath-by-breath method using a MGC respiratory gas exchange analyzer (Medical Graphics, St. Paul, Minnesota). The $VO2_{max}$ was defined as the highest value for or the plateau of oxygen uptake. Reference values for $VO2_{max}$ were based on established reference values derived from a Norwegian cohort.[15] All incident respiratory diseases diseases (defined as COPD, pneumonia, or asthma) that occurred from study entry to 2014 were included. Outcomes were collected by linkage to the National Hospital Discharge Register. The diagnoses of outcomes were made by qualified physicians based on the International Classification of Disease codes. For the current analysis, all men with respiratory diseases (chronic bronchitis, asthma, or tuberculosis) at study entry (n=344) were excluded. Hazard ratios (HRs) with 95% confidence intervals (CIs) were estimated using Cox proportional hazard models. All statistical analyses were conducted using Stata version 14 (Stata Corp, College Station, Texas).

Results

The overall mean [standard deviation (SD)] age and CRF of study participants at baseline were 53 (5) years and 30.7 (8.0) ml/kg/min respectively. A total of 382 hospital diagnosed respiratory diseases were recorded (annual rate 8.86/1000 person-years at risk; 95% CI 8.01 to 9.79) during a median (interquartile range) follow-up of 25.7 (16.9-27.8) years**.** The overall age-adjusted regression dilution ratio of CRF was 0.57 (95% CI: 0.51 to 0.63), which implies that the association of CRF with risk of respiratory disease outcomes using baseline measurements of CRF only, could under-estimate the risk by [(1/0.57)-1]*100 = 75%. Cardiorespiratory fitness was linearly and inversely associated with risk of respiratory disease outcomes after adjustment for several established risk factors (age, smoking status, histories of diabetes and coronary heart disease, years of education, and alcohol consumption) (**Figure**). In age-adjusted analysis, the HR for respiratory disease per 1 SD increase in CRF was 0.66 (95% CI: 0.59 to 0.74), which was minimally attenuated on further adjustment for established risk factors 0.75 (95% CI: 0.66 to 0.85). The association persisted on additional adjustment for total energy intake, socioeconomic status, physical activity, and C-reactive protein 0.81 (95% CI: 0.71 to 0.92). Comparing the extreme quartiles of CRF levels, the corresponding adjusted HRs were 0.40 (95% CI: 0.29 to 0.55), 0.53 (95% CI: 0.38 to 0.74), and 0.63 (95% CI: 0.45 to 0.88) respectively. Correction for within-person variability in CRF levels strengthened the respective associations (**Table**). Given that pneumonia is a transient condition, a separate analysis of the association between CRF and pneumonia was conducted. Cardiorespiratory fitness was inversely associated with risk of pneumonia in a graded dose-response fashion. In a comparison of extreme quartiles of CRF levels, the HR for pneumonia was 0.58 (95% CI: 0.41 to 0.80) in analysis adjusted for several established risk factors for pneumonia. The association remained consistent on further adjustment for total energy intake, socioeconomic status, physical activity, and C-reactive protein 0.67 (95% CI: 0.48 to 0.95).

Discussion

In this first prospective evaluation of the association between CRF and risk of respiratory outcomes in middle-aged Caucasian men who had no apparent pre-existing respiratory diseases at baseline, the findings showed an inverse and dose-response relationship between CRF and future risk of respiratory diseases (defined as COPD, pneumonia, or asthma). The association was independent of several risk factors for these outcomes. A subsidiary analysis showed CRF to be inversely associated with risk of pneumonia in a graded dose-response fashion. Though these diseases are as a result of an interplay of environmental and genetic factors, inflammatory processes mainly underlie their pathogenesis.[5,16] The protective association demonstrated between CRF and respiratory diseases may also be exerted via the anti-inflammatory effects of regular physical activity.[17] Our current findings suggest that regular physical activity, which promotes good CRF levels, may be able to reduce the risk of respiratory diseases in the general population. Indeed, it has been consistently shown that physical activity protects against the development of chronic disease outcomes.[8,9] However, further research is needed to replicate these findings, elucidate the mechanistic pathways involved, and whether information on CRF levels can be used to identify individuals at high risk of respiratory diseases in clinical practise.

Our analysis employed a large-scale population-based prospective cohort design with inclusion of men who were representative of the general population and were free of any diagnosed respiratory diseases at baseline; follow-up was long and complete for all participants; and the analysis was comprehensive which included adjustment for several potential confounders, assessment of the dose-response relationship between the exposure and outcome, as well as correction for within-person variability in CRF levels. The results should be interpreted with caution given the limitations of: (i) the inability to generalise the findings to women and other populations; (ii) the possibility of residual confounding given the observational design, and (iii) the broad classification of combined outcomes.

In conclusion, CRF is strongly and independently associated with reduced risk of respiratory diseases in a graded dose-response fashion in middle-aged Caucasian men. The prognostic value of CRF for long-term risk of respiratory diseases warrants evaluation.

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Compliance with Ethical Standards:

Funding This study was funded by The Finnish Foundation for Cardiovascular Research, Helsinki, Finland.

Conflict of Interest None

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent Informed consent was obtained from all individual participants included in the study.

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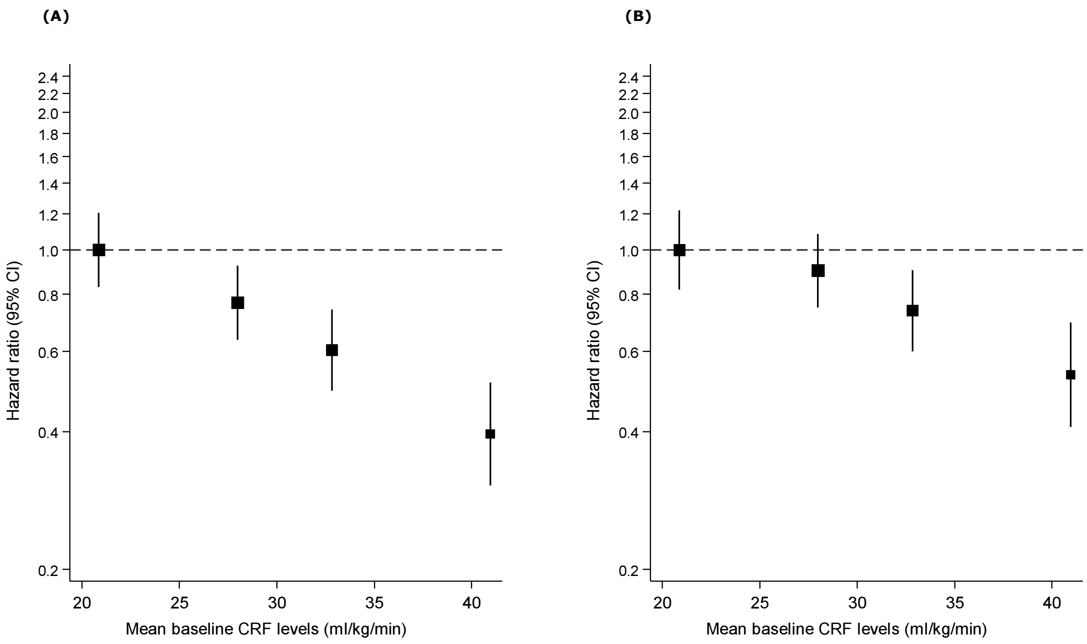
Figure legend

Figure. Hazard ratios for respiratory diseases, by quartiles of baseline levels of cardiorespiratory fitness



A, adjusted for age; **B**, adjusted for age, smoking status, history of diabetes, prevalent coronary heart disease, years of education, total cholesterol, and alcohol consumption

CRF, cardiorespiratory fitness

Table. Association of cardiorespiratory fitness and risk of respiratory diseases

CRF (ml/kg/min)	Events/ Total	Model 1		Model 2		Model 3	
		HR (95% CI)	*P*-value	HR (95% CI)	*P*-value	HR (95% CI)	*P*-value
Baseline CRF							
Per 1 SD increase	382 / 1,974	0.66 (0.59 to 0.74)	< 0.001	0.75 (0.66 to 0.85)	< 0.001	0.81 (0.71 to 0.92)	0.001
Q1 (6.36-25.48)	122 / 494	ref		ref		ref	
Q2 (25.49-30.41)	109 / 493	0.77 (0.59 to 0.99)	0.045	0.90 (0.69 to 1.18)	0.439	0.95 (0.73 to 1.24)	0.713
Q3 (30.41-35.55)	91 / 494	0.60 (0.46 to 0.80)	< 0.001	0.74 (0.55 to 0.98)	0.037	0.85 (0.63 to 1.14)	0.273
Q4 (35.56-65.40)	60 / 493	0.40 (0.29 to 0.55)	< 0.001	0.53 (0.38 to 0.74)	< 0.001	0.63 (0.45 to 0.88)	0.008
Usual CRF*							
Per 1 SD increase	382 / 1,974	0.48 (0.39 to 0.59)	< 0.001	0.60 (0.49 to 0.75)	< 0.001	0.69 (0.55 to 0.86)	0.001
Q1 (6.36-25.48)	122 / 494	ref		ref		ref	
Q2 (25.49-30.41)	109 / 493	0.63 (0.40 to 0.99)	0.045	0.83 (0.52 to 1.33)	0.439	0.92 (0.57 to 1.47)	0.713
Q3 (30.41-35.55)	91 / 494	0.41 (0.25 to 0.67)	< 0.001	0.58 (0.35 to 0.97)	0.037	0.75 (0.45 to 1.26)	0.273
Q4 (35.56-65.40)	60 / 493	0.20 (0.11 to 0.35)	< 0.001	0.33 (0.18 to 0.60)	< 0.001	0.44 (0.24 to 0.81)	0.008

CI, confidence interval; CRF, cardiorespiratory fitness; HR, hazard ratio; ref, reference; Q, quartile; SD, standard deviation;
*, indicates correction for within-person variability in values of CRF, that is, the extent to which an individual's CRF measurements vary around a long-term average value ("usual CRF values")
Model 1: Adjusted for age
Model 2: Model 1 plus smoking status, history of diabetes, prevalent coronary heart disease, years of education, total cholesterol, and alcohol consumption
Model 3: Model 2 plus total energy intake, socioeconomic status, physical activity, and C-reactive protein